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Invention: **Polycyclic pyrimidine-2,4(1H,3H)-diones with functionalized alkyl residues at the 1- and/or 3-position(s); methods for their synthesis and pharmaceutical preparation**

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CLEAN VERSION OF THE AMENDED CLAIMS

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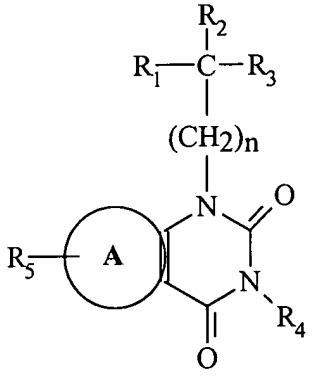
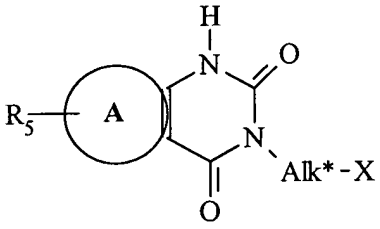
1. A polycyclic (pyrimidine-2,4(1H,3H)-dione) with functionalized alkyl groups in the 1-, 3-, or both positions with the general structures Ia and Ib,



(Ia)



(Ib)

where:

R^1 is hydrogen, methyl, or ethyl

R^2 is hydrogen or methyl

R^3 is mercapto or hydroxyaminoacylalkylthio (-SAlkCONHOH)

Alk is alkyl (C_1-C_5, branched and unbranched)

R4 is hydrogen, benzyl, or phenyl

n is 0, 1 or 2,

Alk* is alkylene {C_2-C_{12}; branched or unbranched, with the exception of 3-methylpropylene [$-CH_2-CH_2-CH(CH_3)-$] }

X is mercapto or hydroxyaminoacylalkylthio (-SAlkCONHOH)

A is an annealed benzene ring

or

a 2,3-annealed thiophene ring, which may in the 4,5-positions be substituted with methyl groups or annealed with a cyclopentene, cyclohexene, or cycloheptene rings,

R^5 is hydrogen, 6-methyl, 8-methyl, 6-fluoro, 6-chloro, 6-bromo, 6-methylthio, or 6,7-dimethoxy,

as well as the tautomers and pharmacologically relevant salts of these compounds.

A1

3. The method for the synthesis of compounds with general structures Ia, Ib, IIa, and IIb, as described in claim 1, are distinguished by the following procedures:

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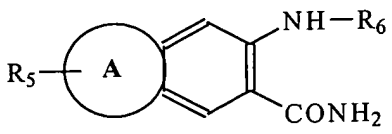
(A) The reaction of 2-(alkenylamino)-1-carbonic acid amides of the general structure III,



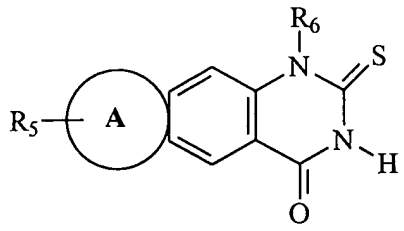
(III)

where R^6 is alkenyl (C_3-C_6), for example allyl, methallyl, crotyl, 1-buten-4-yl, 3-penten-1-yl, and 3-hexen-1-yl, where A and R^5 are as defined above, with a -C=S structural element-donating reagent, such as thiophosgene, thiourea, ammonium or alkalithiocyanate/hydrochloric acid, 1,1'-thiocarbonylbisimidazole, or preferably benzoylisothiocyanate in a polar aprotic solvent,

A2

- stir the reaction mixture
- remove solvent under vacuum,
- add dilute alkali solution and heat gently to *ca.* 60°C,
- separate the insoluble material by filtration,

- cool and acidify the filtrate,
- heat the resulting compound with the general structure IV,

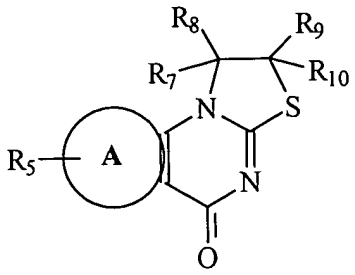


(IV)

A2

where A, R5, and R6 are as defined above,

- with concentrated mineral acid, such as hydrochloric acid, hydrobromic acid and/or sulfuric acid, or mixtures of these mineral acids with glacial acetic acid and or formic acid to reflux,
- cool the reaction mixture,
- dry the recovered compound of the general structure V,

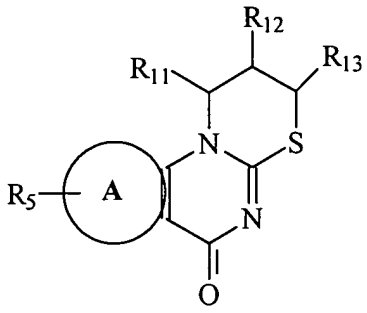


(V)

where

A2 R^7, R^8, R^9, R^{10} are hydrogen, methyl, or ethyl, and A and R^5 are as defined above,

- or dry the recovered compound of the general structure VI,



(VI)

where R^{11}, R^{12}, and R^{13} are hydrogen, methyl, or ethyl, and A and R^5 are as defined above,

- in a vacuum desiccator over potassium hydroxide or
- stir the above compounds in a dilute aqueous sodium carbonate solution,
- isolate the compound,
- heat the compound with dilute mineral acid, such as hydrochloric acid,
- hydrobromic acid and or sulfuric acid, or mixtures f these mineral acids with glacial acetic acid and/or formic acid to reflux,
- cool the reaction mixture,

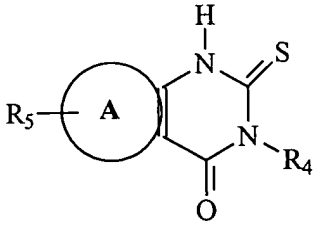
- wash and dry the crystallized product to obtain compounds of the general structure Ia or its tautomers, where R^4 is without exception hydrogen,

wherein the method is described in this invention for the preparation of compounds of the general structure Ia,

where R^3 is mercapto, R^4 is hydrogen, Alk, benzyl, or phenyl, n=1 or 2, and Alk, A, and R^5 are as defined above, is characterized by the following procedures:

A2

B) The reaction of bi- and tricyclic 3-alkyl (or benzyl or phenyl)-pyridin-4(3H)-on-2(1H)-thiones of the general structure VII,



(VII)

where R^4 is hydrogen, benzyl, phenyl, or Alk, and A and R^5 are as described above,

with 1,ω-dihalogenalkanes of the general structure VIII,

$$Hal(CH_2)_mHal$$

where

m is 2, 3, or 4, and Hal is chlorine, bromine, or iodine,

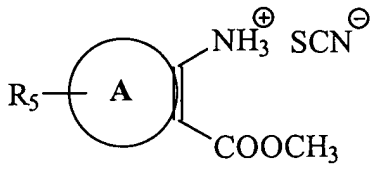
- in an aprotic dipolar solvent, preferably dimethylformamide with the addition of potassium carbonate, with extensive stirring at room temperature,
- add dilute hydrochloric acid,
- heat slowly and thoroughly to reflux,

- filter the reaction mixture,
- cool and store the filtrate at 4°C,
- yields the compound of structure Ia,

where R^3 is mercapto, R^4 is hydrogen, Alk, benzyl, or phenyl; and Alk, A, and R^5 are as defined above,

or

A2 C) the reaction of 2-ammoniun carboxylic acid methyl ester thiocyanate of the general structure IX,



(IX)

where A and R^5 are as defined above,

with 1,ω-dihalogenalkanes of the general structure VIII,

where

m is 2 or 3, and Hal is chlorine, bromine, or iodine,

- heat the reaction partners with stirring until reflux,
- cool and isolate the precipitate,
- wash with diethylether and dry,
- dissolve the precipitate with water,
- filter the solution and add dilute sodium hydroxide to pH 10,
- isolate the precipitate and wash with water,
- dry the precipitate and shake intensively with chloroform,
- isolate the precipitate and dry,
- recrystallize from solvent, preferably 2-methoxyethanol,

to obtain compounds with the general formula V,

obtained from reaction with dibromomethane,

where R^7, R^8, R^9, and R^{10} are hydrogen, and A and R^5 are as described above,

or the compound of the general structure VI,

A2 obtained from reaction with 1,3-dibromopropane

where R^{11}, R^{12}, and R^{13} are hydrogen, and A and R^5 are as described above,

heating the compounds obtained above of the general structures V or VI in dilute mineral acids, such as hydrochloric acid, hydrobromic acid and or sulfuric acid, or mixtures of these mineral acids with glacial acetic acid and/or formic acid to reflux,

- cool the reaction mixture,

- wash and dry the crystallized material to obtain compounds of the general structure Ia or its tautomers,

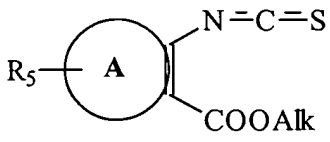
where R^1, R^2, R^4 are hydrogen, R^3 is mercapto, n = 1 or 2, and A and R^5 are as defined above,

wherein the method is described in this invention for the preparation of compounds of the general structure Ib,

A2

where Alk* is n-butylene ($-CH_2-CH_2-CH_2-CH_2-$), X is mercapto, and A and R^5 are as defined above,
is characterized by the following procedures:

D) The reaction of 2-isothiocyanato-1-carboxylic acid ester of the general structure X,



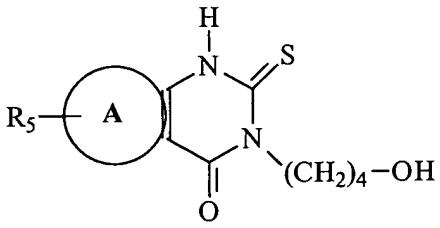
(X)

where Alk, A, and R^5 are as defined above,

with 4 aminobutan-1-ol at room temperature with intensive and extensive stirring

- add water to obtain compounds of the general structure XI,

A2



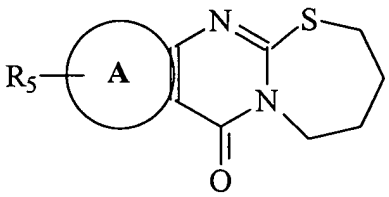
(XI)

where A and R^5 are as defined above,

- react compounds of the general structure XI with concentrated mineral acids, such as hydrochloric acid, hydrobromic acid and or sulfuric acid, or mixtures of these mineral acids with glacial acetic acid and/or formic acid to reflux,
- cool the reaction mixture and isolate the crystalline precipitate,

A2

- add aqueous sodium carbonate to the precipitate to adjust pH to *ca.* 9,
- isolate the crystalline precipitate, wash with water, and dry to obtain polycyclic 2,3,4,5-tetrahydro-7H-[1,3]thiazepin0[2,3-a]pyrimidin-7-one or the general structure XII,



(XII)

where A and R^5 are as defined above,

Heat the above mentioned compounds of the general structure XII in extremely dilute mineral acids, such as hydrochloric acid, hydrobromic acid and or sulfuric acid, or mixtures of these mineral acids with glacial acetic acid and/or formic acid to reflux,

- cool the reaction mixture,
- wash and dry the crystalline precipitate

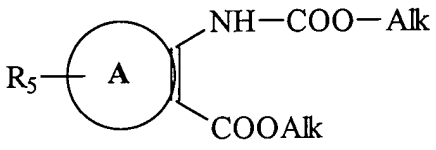
to obtain compounds of the general structure Ib or their tautomers,

where Alk* is n-butylene ($-CH_2-CH_2-CH_2-CH_2-$), X is mercapto, and A and R^5 are as defined above,

wherein the method is described in this invention for the preparation of compounds of the general structure Ib, where Alk* is alkylene {C_2-C_{12}; branched or unbranched, with the exception of 3-methylpropylene [$-CH_2-CH_2-CH(CH_3)-$] } , X is

mercapto, and A and R^5 are as defined above, is characterized by the following procedures:

E) The reaction of 2-alkoxycarbonylamino-1-carboxylic acid alkyl ester of the general structure XIII,



(XIII) **H_2NAlk^*OH** **(XIV)**

where Alk is alkyl (C_1-C_3) and A and R^5 are as defined above,

with aminoalkanols of the general structure XIV,

where Alk* is alkylene {C_2-C_{12}; branched or unbranched, with the exception of 3-methylpropylene [$-CH_2-CH_2-CH(CH_3)-$] },

by heating in well-known reactions,

- cool the reaction mixture,
- add water and dilute hydrochloric acid to *ca.* pH 4,
- isolate the precipitate, wash with water, and dry to obtain the polycyclic 3-(ω-hydroxyalkyl)-pyrimidine-2,4(1H,3H)-diones of the general structure XV,

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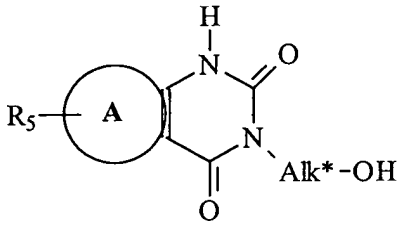


(XVI)

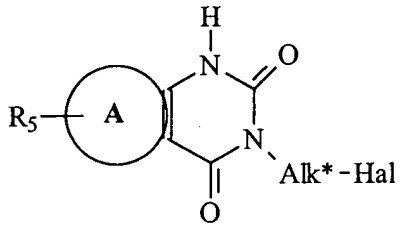
where Alk* is alkylene {C_2-C_{12}; branched or unbranched, with the exception of 3-methylpropylene [-CH_2-CH_2-$CH(CH_3)$-] } and

A and R^5 are as defined above,

reacting the compounds of the general structure XV with concentrated hydrochloric acid, phosphorus trichloride, or phosphoroxidchloride, but preferably with concentrated hydrobromic acid by

- heating to reflux,
- cooling the reaction mixture,
- isolating the precipitate, washing with water and drying to obtain polycyclic 3- (ω-haloalkyl)-pyrimidin-2,4(1H,3H)-diones of the general structure XVI,

A2



(XVII)

where Hal is chlorine, or bromine, and Alk*, and A and R^5 are as defined above.

React the compounds of the general structure XVI in rapidly boiling polar solvent with thiourea,

- heat to reflux,
- cool the reaction mixture,
- add water and dilute aqueous sodium hydroxide to obtain an alkaline pH,
- after the solution clears, filter it and
- add to the filtrate dilute hydrochloric acid to *ca*. pH 3,
- isolate the precipitate, wash with water, and dry to obtain compounds of the general structure Ib or their tautomers,

where Alk* is alkylene {C_4-C_{12}; branched or unbranched, with the exception of 3-methylpropylene [$-CH_2-CH_2-CH(CH_3)-$] }, X is mercapto, and A and R^5 are as defined above,

wherein the method is described in this invention for the preparation of compounds of the general structure Ia or Ib, where R^3 or X is hydroxaminoacylalkylthio (-SAlkCONHOH) and R^1, R^2, R^4, Alk, n, Alk*, A, and R^5 are as defined above,

is characterized by the following procedures:

A2

F) React compounds of the general structure Ia or Ib,

where R^3 is mercapto, and R^1, R^2, R^4, Alk, n, Alk*, A, and R^5 are as defined above,

with N-hydroxyhalogencarboxylic acid amide, preferably 2-chloro-N-hydroxyacetamide ($ClCH_2CONHOH$),

- either in pyridine
- or in acetone solution, preferable in the presence of base,
- at room temperature,
- remove solvent by distillation,

- add water,
- isolate the precipitate, wash with water and dry to obtain compounds with the general structure Ia or Ib or their tautomers,

where R^3 or X is hydroxyaminoacylalkylthio.

4. A method based on claim 3, characterized by one or more of the following steps:

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a) the reaction of compounds of general structure III with benzoylisothiocyanate in absolute acetone,

b) the reaction of compounds of general structure VII with compounds of general structure VIII in absolute dimethylformamide with dry potassium carbonate.

5. A pharmaceutical preparation containing one or more compounds in claim 1 , as well as commonly used filler and inert ingredients, and binders.

A2

6. A pharmaceutical preparation with collagenase/MMP-inhibiting activities, thus characterized by the fact that they contain as active ingredients one or more compounds covered by claim 1.